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Letter to the Editor in response to the original article: Preventive Antiepileptic Treatment in Tuberous Sclerosis Complex: A Long-Term, Prospective Trial, by Józwiak et al.
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Prophylactic Antiepileptic Treatment in Tuberous Sclerosis

Jóźwiak et al.¹ suggest that their study, “...provides evidence that preventive antiepileptic treatment in infants with tuberous sclerosis complex improves long-term epilepsy control and cognitive outcome at school age.” The study is problematic, however, because it compares two groups that have been ascertained in entirely different ways: the “Standard” group after presentation with TSC and usually epilepsy; and the “Preventive” group with suspected or proven TSC but without epilepsy.

In the Preventive group, 11 infants received antiepileptic treatment in anticipation of any seizures, and four in that group did not develop seizures. Three infants in that group did not receive preventive treatment, but neither did they develop seizures. One could argue that they were managed in the standard fashion and that their IQs should have been analyzed as part of the outcomes in the Standard group. Instead, the authors have adopted an implicit intention-to-treat analysis in a situation where the study is descriptive and there has been no element of randomization.

The fact that one-fifth of those cases did not develop epilepsy despite failing to receive the preventive treatment highlights the likelihood of there being a significant ascertainment bias at play. The likely impact of such bias or misclassification is illustrated by the relative paucity of observations in the Preventive group (see figure 1).

Table 3 of the study presented both median and mean IQs for these groups, but the *P*-values do not seem to be derived from the nonparametric statistical tests promised in the Methods section. Based on the IQ data from tables 1 and 2, for example, a two-sample Wilcoxon rank-sum test on the main IQ analysis gives $P=0.046$ ($z=1.997$). And the same test performed after moving the IQ result for case 14, which had not received preventive treatment, to the Standard group gives $P=0.081$ ($z=1.747$). Therefore, even if the appropriate independence and distributional assumptions had been valid, a sensitivity analysis shows the result to be at best of borderline statistical significance.

Finally, there is a question of the biological plausibility of the findings. We are excited by the idea of identifying a preventive strategy that will help to improve such outcomes, but most clinicians will find it hard to believe that this intervention resulted in an improvement in median IQ of 48 points.

We look forward to the results of further studies in this area.

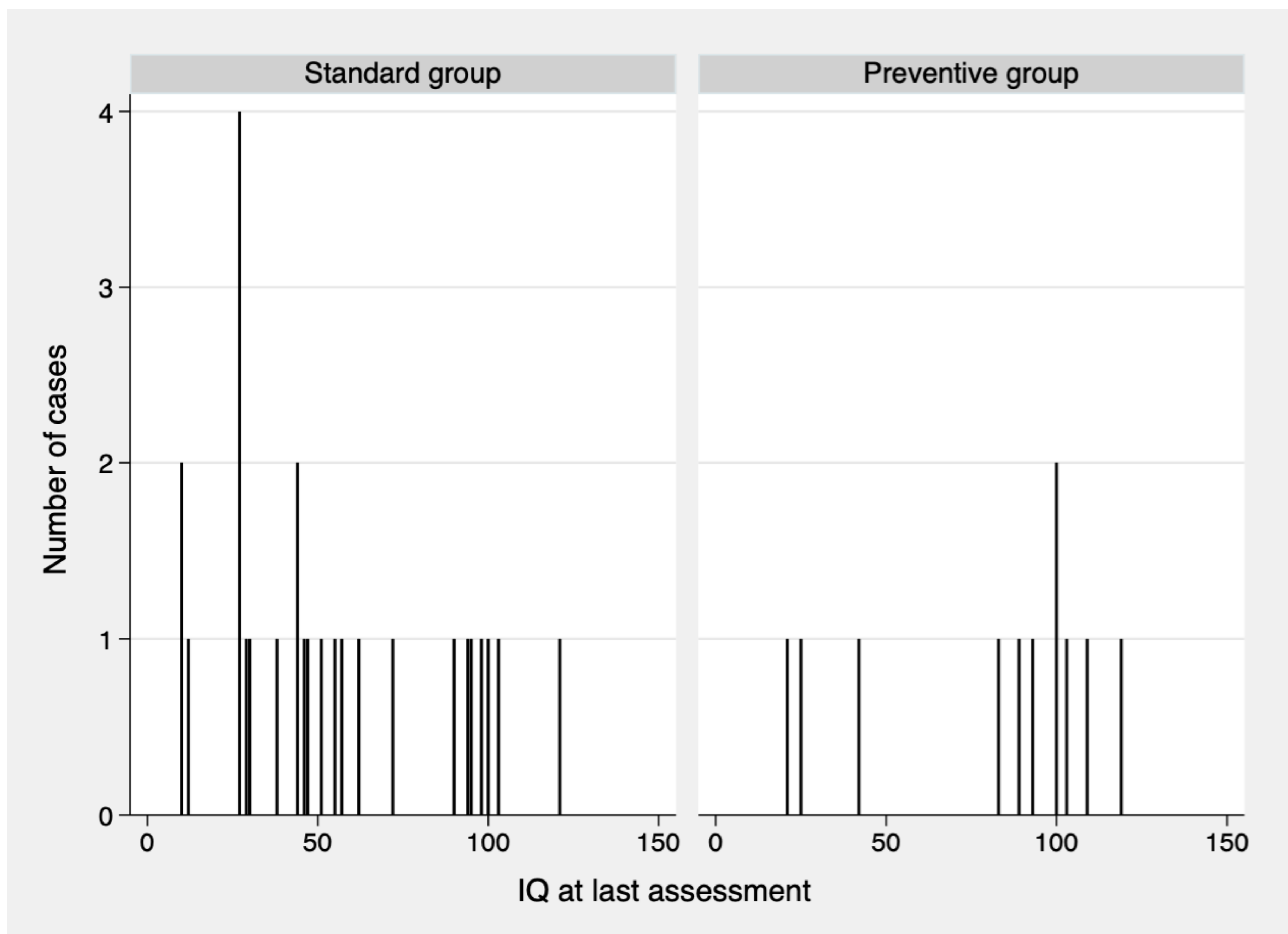


Figure 1: Distribution of IQ at last assessment in Standard and Preventive groups.

Reference:

1. Jozwiak S, Słowińska M, Borkowska J et al. Preventive Antiepileptic Treatment in Tuberous Sclerosis Complex: Long-Term, Prospective Trial. *Pediatr Neurol.* 2019;101:18-25. <https://doi.org/10.1016/j.pediatrneurol.2019.07.008>